Synthesis of trialkyl 2-halogeno-1,1,1-ethanetricarboxylates

Juan Zinczuk* and Gustavo A. Carnavale

Instituto de Química Rosario (CONICET-UNR . Facultad de Ciencias Bioquímicas y Farmacéuticas Universidad Nacional de Rosario. Suipacha 531- 2000 Rosario - Argentina
E-mail: jzinczuk@fbioyf.unr.edu.ar

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Abstract

A series of trialkyl 2-halogeno-1,1,1-ethanetricarboxylates (Hal = Cl, Br, I) was obtained in high yields by halomethylenation of trialkyl methanetricarboxylates that in turn were derived from dialkyl malonates. The variables that control the reaction (solvent, temperature, time of reaction, base, and alkylating agent) were adjusted to optimize the yield. This new family of compounds may be considered as synthetic equivalents of the unstable dialkyl (halomethyl)malonates.

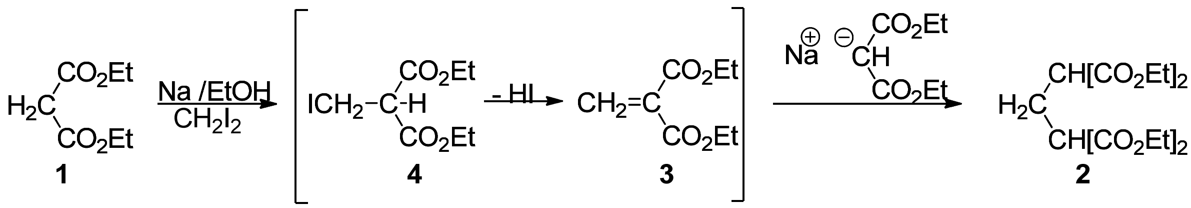
Keywords: Halomethylenation, dialkyl (halomethyl)malonates, trialkyl 2-halogeno-1,1,1-ethanetricarboxylates, optimized synthesis.

Introduction

We are interested in the reactivity of metallic homoenolates, formally derived from dialky methylmalonates, and proposed the metallation of the appropriate dialkyl (halomethyl)malonates as a method of preparation. Dialkyl (halomethyl)malonates are scarcely referenced in the literature. The only reported example corresponds to diethyl (bromomethyl)malonate, obtained in impure form by Simonsen by reaction of diethyl (2-methoxymethyl)malonate and hydrobromic acid.[1] More recently Dowd and Shapiro improved the compound purity but recognized the sensible nature of the bromo compound.[2]

The study of the halomethylenation of dialkylmalonates began more than a century. The reaction of diethyl malonate (**1**) and diiodomethane in the presence of sodium ethoxide was first reported by Guthzeit and Dressel in 1888.[3,4] They used a half equivalent of diiodomethane and obtained 84% of tetraethyl 1,1,3,3-propanetetracarboxylate (**2**).

Perkin and Prentice obtained the same compound in 60% yield replacing diiodomethane by dichloromethane and conducted the reaction in a closed vessel.[5] In turn, F. Tutin carried out the reaction under identical conditions but obtained only 20% of product.[6] Using diiodomethane in place of dichloromethane he obtained a mixture of unreacted **1** and diethy methylenemalonate (**3**). The expected **2** was not detected. N. Zielinsky also investigated the reaction using a 1:1:1 molar ratio of **1**, diiodomethane and sodium ethoxide and postulated the intermediate formation of diethyl (iodomethyl)malonate (**4**), which under the reaction conditions eliminates HI to give **3** that, in turn, suffers Michael addition by the anion of **1** to yield **2** (Scheme 1).[7]

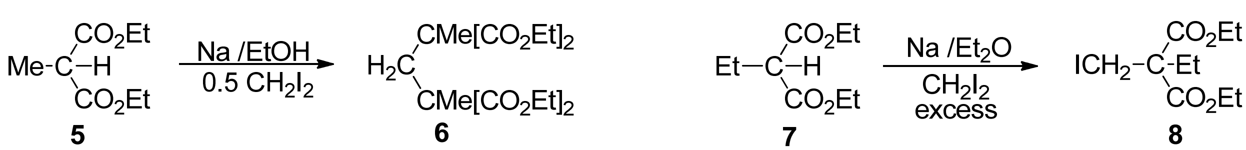


Scheme 1. Reaction of diethyl malonate with diiodomethane.

We have carried out the reaction using similar conditions and analyze the products by gas chromatography-mass spectrometry. Only three peaks are observed that correspond to diodomethane (13%), **2** (84%) and a product of condensation of diiodomethane and three molecules of **1** (3%).

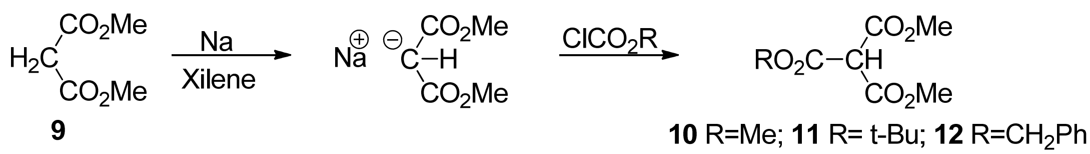
As a conclusion, the compounds obtained by the condensation of dihalomethanes and the sodium enolate of **1** vary according to the conditions under which the reaction takes place, but in no case, the diethyl (halomethyl)malonate could be detected because, under the basic conditions of the reaction, the methinic hydrogen atom is removed together with the halogen atom and the generated **3** is attacked by the anion of **1**. For this reason, it is necessary to replace an acidic methylenic hydrogen atom of the dialkyl malonate by an effective protecting group previous to halomethylenation. As a model we analyzed the reactions of dialkyl alkylmalonates with diiodomethane.

The products of the reaction depend on the reaction conditions and the proportions of reagents. Thus, Auwers and Thorpe reported the reaction of diiodomethane, diethyl methylmalonate (**5**) and sodium ethoxide in ethanol using a 1:2:2 ratio to give tetraethyl 1,3-dimethyl 1,1,3,3-propanetetracarboxylate (**6**).[8] In turn, Kötz and Zörnig reacted diethyl ethylmalonate (**7**) and sodium in ether and then with an excess of diiodomethane to obtain diethyl (2-iodomethyl)ethylmalonate (**8**) (Scheme 2).[9]



Scheme 2. Reaction of diethyl alkylmalonates with diiodomethane.

In view of these results, we decided to substitute one methylenic hydrogen atom of the dialkyl malonate by an effective protecting group that could be easily deblocked at the final stage of the reaction. Following the strategy developed by Rapoport et al.[10] we choose an alkoxycarbonyl group as the protecting group (Scheme 3).

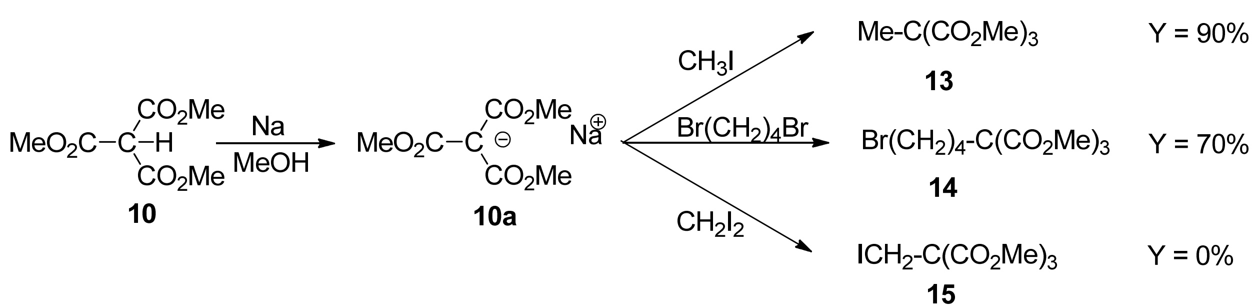


Scheme 3. Preparation of trialkyl methanetricarboxylates.

The resulting trialkyl methanetricarboxylates obtained in high yield from dialkyl malonate and the appropriate alkyl chloroformate[11] may be viewed as a synthetic equivalent of the original dialkyl malonate, with the advantage that there is only one acidic hydrogen atom to be eliminated under basic conditions to form the corresponding enolate which is an appropriate substrate for the halomethylenation reaction.

For practical reasons, starting with dimethyl malonate (**9**), we use three different protecting group alternatives: 1) methoxicarbonyl group to generate the high symmetric trimethyl methanetricarboxylate (**10**). This group can be deprotected by different reagents,[10] for example with boron trichloride in dichloromethane at 5 ^{o}C, 2) tert-butoxycarbonyl (BOC) group to give tert-butyl dimethyl methanetricarboxylate (**11**) that can be deprotected selectively by acidic work-up, and 3) benzyloxycarbonyl (CBZ) group to give benzyl dimethyl methanetricarboxylate (**12**) that allow their selective cleavage by hydrogenolysis.

The trialkyl methanetricarboxylates are easily converted into the sodium or potassium salt by the reaction with the respective metal alkoxides. The resulting enolates are readily alkylated in high yield with alkyl halides or sulfates in different solvents such as acetone, dioxane and a 1:1 mixture of benzene and dimethylformamide (DMF).[10-15] Thus, for example, trimethyl sodiomethanetricarboxylate (**10a**) or trimethyl potassiomethanetricarboxylate (**10b**) reacts with iodomethane in dioxane at reflux to give 90% of trimethyl 1,1,1-ethanetricarboxylate (**13**) [14] and **10a** reacts with 1,4-dibromobutane in a 1:1 mixture of benzene and DMF at 80 ºC for 20 h to give trimethyl 5-bromopentane 1,1,1-tricarboxylate (**14**) in 70% yield.[10] (Scheme 4).



Scheme 4. Reaction of trialkyl methanetricarboxylates with haloalkanes.

Results and Discussion

Halomethylenation of trialkyl methanetricarboxylates.

Applying the conditions mentioned above to methylating (**10a**) but using diiodomethane as alkylating agent, we observed that no trimethyl 2-iodo-1,1,1-ethanetricarboxylate (**15**) was formed (Scheme 4).

This striking reactivity difference could be mainly attributed to the heterogeneous character of the reaction and the great size and different reactivity of the diiodomethane as alkylating agent. To improve the halomethylenation we analyzed the main factors that could affect the reaction including the solvent, temperature, time of reaction, and the base used.

(i) Solvent. **10a** is sparingly soluble in dioxane, ether, benzene and other solvents of low polarity and no reaction with diiodomethane in these solvents was observed. Otherwise, polar solvents are expected to solubilize the salt and facilitate the reaction. Polar protic solvents like methanol, though they solubilize the salt, are inappropriate because they protonate or solvate the anion through hydrogen bonds and reduce their basic and nucleophilic character. On the other hand, aprotic polar solvents like DMF and dimethylsulfoxide (DMSO) easily solubilize the salt but solvate poorly the anion that enhances its nucleophilic character.[16]

The effects of solvent on the yield of **15** are given in Table 1.

Table 1. Reaction of **10a** and **10b** with diiodomethane

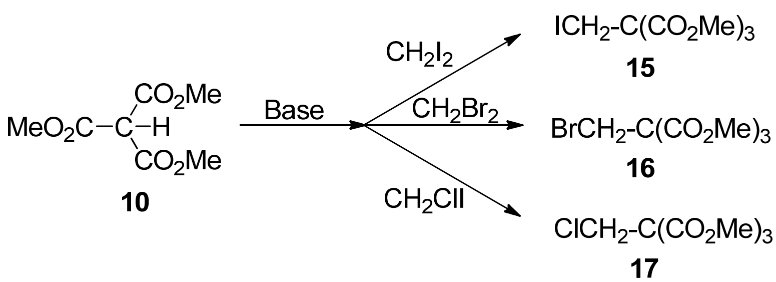
Solvent	Substrate	Time [h]	Temp.[^{o}C]	**15** %Yield
Dioxane	**10a**	12	100	0
Methanol	**10a**	12	60	0
THF	**10a**	12	66	0.3
Benzene-DMF 1:1	**10a**	12	70	27
DMF	**10a**	12	60	39
DMSO	**10a**	12	70	61
DMSO	**10b**	12	70	71

The homogeneous reaction carried out in DMF yields 39% of **15**, whereas in DMSO the yields are 61% for **10a** and 71% for **10b**. This difference may be attributed to the more nucleophilic enolate anion of **10** when potassium is the counter metal cation.

(ii) Temperature and time. The range of temperature was varied between 20 and 100 ^{o}C and the reaction time between 3 and 30 h. Based on the experimental results, we fixed the optimal values at 70 ^{o}C and 12 h respectively.

(iii) Salt preformation versus in situ formation. A new alternative procedure to the use of **10a** or **10b** in the halomethylenation reaction, starts from **10** and an appropriate base to generate the corresponding anion. The *in situ* formed enolate, depending on the base used, would be associated with different counter metal cations as ion pairs. The rate of halomethylation would depend on the extension of this association which is a function of the particular cation employed.

Compound **10** is a relative acidic compound with a pKa = 7.8 and a moderate strong base is enough to deprotonate and form its enolate, previous to reaction with dihalomethanes. (Scheme 5).



Scheme 5. Improved synthesis of trimethyl 2-halogeno-1,1,1-ethanetricarboxylates.

Several bases were compared for the reaction of **10** and dibromomethane in DMSO. The results are listed in Table 2.

Table 2. Base effects on the yield of **16** by reaction of **10** and CH_2Br_2 in DMSO at 70 ^{o}C for 12 h

Base	pKa	**16** %Yield (*)
DBN	12.7	36
MeONa	15.5	34
Li_2CO_3	10.3	21
Na_2CO_3	10.3	69
K_2CO_3	10.3	94
Cs_2CO_3	10.3	96

(*) analyzed by GC-Mass spectrometry.

The reaction of **10** and CH_2Br_2 using 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) gives a mixture of 36% of the desired **16**, 12% of the starting **10** and several other condensation products between **10** and **16**. With sodium methoxide the yield of the product also is low (34%). The main coproduct corresponds to **13** (49%), the reduction product of **16**. The use of alkaline carbonates gives yields between 21 and 96%. The higher yields correspond to potassium and cesium carbonate.

(iv) Effect of counterion. A comparison of the product yields using as base alkaline carbonates, shows that the reactivity of the enolate ion is influenced by the nature of the counter metal cation.

Lithium cation forms the more tightly associated enolate-cation ion pair that reduces its nucleophilicity. The more reactive free enolate anions are likely to predominate in dipolar aprotic solvents that solvate the cation but leave free the enolate anion. In this way, the less associated potassium or cesium enolates are the more reactive and give **16** in excellent yield. As expected, sodium carbonate as a base gives an intermediate yield.

(v) Effect of the halogen. The reactivity of various dihalomethanes as alkylating agent for **10** correlates with the order observed for other bimolecular nucleophilic displacement reactions. The iodide is slightly more reactive than the bromide which is much more reactive than the chloride. Applying the optimal conditions previously established for the reaction of **10** and dibromomethane, several trialkyl 2-halogeno-1,1,1-ethanetricarboxylates were obtained. The results are summarized in Table 3.

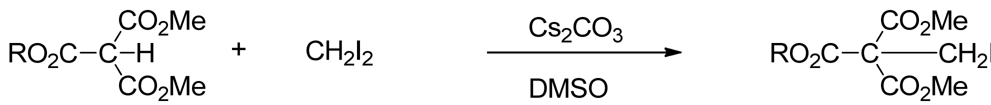
Table 3. Yields of trialkyl 2-halogeno-1,1,1-ethanetricarboxylates

Substrate	Base	Dihalomethane	Product	%Yield
10	K_2CO_3	CH_2I_2	**15**	95
10	Cs_2CO_3	CH_2I_2	**15**	97
10	Cs_2CO_3	CH_2Cl_2	**17**	1.3
10	K_2CO_3	CH_2ClI	**17**	89
10	Cs_2CO_3	CH_2ClI	**17**	84
10	Cs_2CO_3	CH_2Br_2	**16**	96
10	Cs_2CO_3	CH_2BrI	**15**	54
			16	40
11	Cs_2CO_3	CH_2I_2	**18**	92
12	Cs_2CO_3	CH_2I_2	**19**	74

Diiodomethane reacts with **10** and the potassium or cesium carbonate in DMSO with yields comparable to dibromomethane, whereas dichloromethane, even in a closed vessel, only yields 1.3% of **17**. The replacement of dichloromethane by chloroiodomethane that implies the change of the poor nucleofuge chloride by the effective iodide,[17] increases the yield of **17** to 89%.

The reaction of **10** and bromoiodomethane shows a competitive displacement between both halogen atoms with a preference for the bromo atom. This preference may be adscribed to the great size of the iodo atom in a reaction with a crowded transition state.

The iodomethylenation reaction was extended to **11** to give **18** and **12** to give **19** also with high yields.[18]



11 R= t-Bu; **12** R=CH_2Ph **18** R= t-Bu; **19** R=CH_2Ph

Scheme 6. Synthesis of tert-butyl dimethyl methanetricarboxylate and benzyl dimethyl methanetricarboxylate.

Experimental Section

General. All reactions were performed under a nitrogen atmosphere in anhydrous solvents and dried glassware. The progress of the reactions was monitored by TLC (Merck silica gel 60F 254 and developed with either a UV lamp (λ = 254 nm) or iodine vapor. Flash column chromatography was performed using silica gel 60 (Merck 230-400 Mesh) and hexane- ethyl acetate (90:10) as eluent. Sonications were made in a Testlab cleaning bath, 40 kHz. CG-Mass spectra were recorded on a Shimadzu GCMS-QP2010 Plus or Perkin Elmer autosystem XL GC Spectrometer using SE-30, 25 m x 0.22 mm column. High resolution mass spectrometry analyses were performed with a Bruker Micro TOF Q-11. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer at 300 and 75 MHz, respectively. The chemical shifts are given in ppm downfield from TMS. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA (U.S.A.) and Umymform (Argentina). Melting points were measured on an Electrothermal 9100 apparatus and IR spectra were recorded on a FT IR Shimadzu 8101 spectrometer. Anhydrous dioxane was obtained by refluxing and distillation over sodium wire using benzophenone as indicator. DMSO and DMF were dried and distilled from CaH_2. Bromoiodomethane and chloroiodomethane were prepared according to literature method.[19]

Trimethyl methanetricarboxylate (10).[11] According to literature, **9** and sodium in xylene give the enolate that reacts with methyl chloroformate to yield 40% of **10**. Mp 45 - 46 °C. (Lit.[11] mp 43 - 45 ºC).^{1}H NMR ($CDCl_3$) δ: 3,78 (s, OCH_3, 9H), 4,43 (s, CH, 1H).^{13}C NMR ($CDCl_3$) δ: 53,29 (OCH_3), 58,36 (C 4°), 164,15 (C=O).

Trimethyl sodiomethanetricarboxylate (10a).[10] An equivalent of sodium methoxide in methanol was added to a solution of **10** in anhydrous ether, cooled in an ice bath. The insoluble was washed with ether and dried. Yield 95%.

Trimethyl potassiomethanetricarboxylate (10b). A solution of 2.55 g. (13 mmol) of **10** in 10 mL of anhydrous DMSO was added to a solution of 1.50 g (13 mmol) of potassium tert-butoxide in 50 mL of anhydrous DMSO at rt. The white suspension was stirred for 1 h, centrifugated, the solid washed with hexane and dried in vacuum at 25 ^oC. Yield 2.75 g (93%).

Trimethyl 1,1,1-ethanetricarboxylate (13).[14] To a suspension of 0.212 g (1 mmol) of the **10a** in 5 mL of anhydrous dioxane were added 0.426 g (3 mmol) of iodomethane. The reaction tube was sealed with a Teflon stopper and the mixture sonicated at 70 ^oC during 12 h. No starting material was detected by TLC. The mixture was cooled to rt and poured into 10 mL of water and extracted with ether (3 x 10 mL). The combined ether extracts were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4 and evaporated. The colorless oil product was pure by GC. Yield 0.184 g (90%). ^1H NMR ($CDCl_3$) δ : 1,72 (s, CH_3, 3H), 3,79 (s, OCH_3, 9H). ^{13}C NMR ($CDCl_3$) δ: 18,99 (CH_3), 53,32 (OCH_3), 61,79 (C 4^o), 168,12 (C=O).

***tert*-Butyl dimethyl methanetricarboxylate (11).[10]** To 0.69 g (30 mmol) of sodium sand in 60 mL of THF were added 5.22 g (30 mmol) of tert-butyl methyl malonate. The mixture was stirred and heated at 50 ^oC overnight and then cooled in an ice bath. To the cooled and stirred mixture was added dropwise a solution of 4.27 g (45 mmol) of methyl chloroformate in 10 mL of THF and then heated at 50 ^oC for 1 h, cooled to rt and poured into a mixture of cold citric acid-monophosphate buffer (120 ml) and ether (60 mL). The aqueous layer was extracted with ether (2 x 40 mL) and the combined ether phase washed with water (20 mL), brine (20 mL) and dried over sodium sulfate. The solvent was evaporated and the crude product was purified by distillation as a colorless oil. Bp (0.5 Torr) 100 - 103 ^oC. Yield 4.31 g (62%). Anal. Calcd. for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94. Found: C, 51.65; H, 7.10. ^1H NMR ($CDCl_3$) δ : 1.45 (s, ^{t}-Bu, 9H), 3.77 (s,OCH_3, 6H), (4.32 (s, CH, 1H). ^{13}C NMR ($CDCl_3$) δ : 27.71 (**C**H_3),: 53.09 (O-**C**H_3): 59.61 (C-H): 83.63(O-**C**Me_3): 162.73 (**C**O_2 ^{t}-Bu): 164.60 (**C**O_2Me).

Benzyl dimethyl methanetricarboxylate (12). Dimethyl sodium malonate was prepared by adding a solution of 1.32 g (10 mmol) of dimethylmalonate in 5 mL of toluene to a stirring suspension of 0.23 g (10 mmol) of sodium sand in 10 ml of toluene at reflux. To the cooled (-10 ^oC) and stirred white suspension a solution of 1.88 g (11 mmol) of benzyl chloroformate in 10 mL of toluene was added dropwise, the mixture heated 3 h at rt and then poured into 10 mL of aqueous 2% HCl . The organic layer was washed with water, dried over sodium sulfate and the solvent evaporated to give 2.60 g of crude product as an oil which was purified by column chromatography. Yield of colorless oil : 1.41 g (53%). Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.65; H, 5.30. Found: C, 58.62; H, 5.44. ^1H NMR ($CDCl_3$) δ : 3.77 (s,OCH_3, 6H); (4.49 (s, CH, 1H); 5.24 (s, CH_2-Ph, 2H); 7.34 (m, Ph, 5H). ^{13}C NMR ($CDCl_3$) δ : (53.31 (O-**C**H_3); 58.60 (**C**-H); 68.05 (**C**H_2-Ph); 128.24 (C2',C6'-Ph); 128.56 (C4'Ph); 128.60(C3',C5' Ph); 134.80(C1'Ph); 163.61 (**C**O_2 CH_2-Ph); 164.13 (**C**O_2Me).

Trimethyl 2-chloro-1,1,1-ethanetricarboxylate (17). 0.380 g (2 mmol) of **10** was added to a stirred suspension of 0.652 g (2 mmol) of anhydrous cesium carbonate in 10 mL of DMSO at 70 ^oC. The mixture was stirred at 70 ^oC for 12 h and then treated with 0.706 g (4 mmol) of CH_2ClI. After stirring overnight at 70 ^oC the mixture was cooled to rt and worked-up. Yield 0.400 g

(84%). An analytical sample was obtained by crystallization from isopropyl ether mp 52.5 - 53.5 ^{o}C. By using K_2CO_3 as base the yield increases to 89 %. Anal. Calcd. for $C_8H_{11}ClO_6$: C, 40.25; H, 4.61; Cl, 14.88. Found: C, 40.29; H, 4.53; Cl, 15.01. ^{1}H NMR ($CDCl_3$) δ : 3.81 (s,OCH_3, 9H), 4.06 (s, CH_2, 2H).^{13}C NMR ($CDCl_3$) δ : 43.04 (C-Cl), 53.63 (OCH_3), 66.53 (C 4^{o}), 164.88 (C=O).

Trimethyl 2-bromo-1,1,1-ethanetricarboxylate (16). (a) From **10a**. To 1.060 g (5 mmol) of **10a** in 10 mL of DMSO was added 1.240 g (7 mmol) of CH_2Br_2 and heated with stirring at 70 ^{o}C during 12 h. The mixture was poured into 40 mL of water and extracted with ether (4 x 20 mL). The combined ether extracts were washed with water (10 mL) and brine (10 mL), dried over MgSO4 and evaporated. The crude product was purified by column chromatography. Yield 0.477 g. (33%) mp 66.8 - 67.6 ^{o}C ($^{i}Pr_2O$). Anal. Calcd. for $C_8H_{11}BrO_6$: C, 33.92; H, 3.88; Br, 28.27. Found: C, 33.78; H, 3.75; Br, 27.98. ^{1}H NMR ($CDCl_3$) δ : 3.82 (s, OCH_3, 9H), 3.89 (s, CH_2 2H). ^{13}C NMR ($CDCl_3$) δ : 29.45 (C-Br), 53.66 (O-CH_3), 66.10 (C 4^{o}), 164.99 (C=O).

(b) From **10b**. 1.140 g (5 mmol) of the **10b** in 10 mL of DMSO ws reacted with an excess 2.610 g (15 mmol) of CH_2Br_2 at 70 ^{o}C during 12 h. After usual work-up yield 1.160 g of product (82%).

(c) From **10b**. To a stirred suspension of 0.138 g (1 mmol) of anhydrous potassium carbonate in 5 mL of DMSO at 70 ^{o}C was added 0.190 g (1 mmol) of **10**. The mixture was stirred at 70 ^{o}C for 12 h and then treated with 0.522 g (3 mmol) of CH_2Br_2. After stirring at 70 ^{o}C during 4 h the mixture was cooled to rt and worked-up. Yield 0.266 g (94%). Yields of product using other alkaline carbonates see Table 2.

(d) From bromoiodomethane and **10a**. 1.060 g (5 mmol) of **10a** in 10 mL of DMSO was reacted with 1.105 g (5 mmol) of CH_2BrI at 70 ^{o}C during 20 h. After usual work-up, the crude product was purified by column chromatography. Yield 0.482 g. (34%).

(e) From bromoiodomethane and **10**. To a stirred suspension of 0.326 g (1 mmol) of anhydrous cesium carbonate in 5mL of DMSO at 70 ^{o}C was added 0.190 g (1 mmol) of **10** and the mixture heated 12 h. The cooled mixture was treated with 0.663 g (3 mmol) of CH_2BrI and heated at 70 ^{o}C for 4 h. After usual work-up, the product was isolated and analyzed by GC-mass spectrometry. Only two products were detected: 40% of bromoderivate **16** and 54% of iododerivate **15**.

Trimethyl 2-iodo-1,1,1-ethanetricarboxylate (15). (a) From **10a**. To 1.060 g (5 mmol) of **10a** dissolved in 10 mL of DMSO was added 1.340 g (5 mmol) of CH_2I_2 and the mixture stirred at 70 ^{o}C during 12 h. The solution was cooled to rt and poured into 40 mL of water and extracted with ether (3 x 10 mL). The combined ether extracts were washed with water (10 mL) and brine (10 mL), dried over MgSO4 and evaporated. The crude product (1.544 g) was purified by column chromatography. Yield 1.006 g (61%). mp 57.5 - 58 ^{o}C. An analytical sample was obtained by crystallization from isopropyl ether. Anal. Calcd. for $C_8H_{11}IO_6$: C, 29.11; H, 3.36; I, 38.45. Found: C, 29.33; H, 3.39; I, 38.32. ^{1}H NMR ($CDCl_3$) δ: 3.71(s,CH_2, 2H), 3.84 (s, O-CH_3, 9H). ^{13}C NMR ($CDCl_3$) δ : - 0.37 (C-I), 53.67 (O-CH_3), 65.73 (C 4^{o}), 165,19 (C=O).

(b) From **10** and alkaline carbonates. To a stirred suspension of 0.326 g (1 mmol) of anhydrous cesium carbonate in 5mL of DMSO at 70 ^{o}C was added 0.190 g (1 mmol) of **10**. After 12 h the mixture was cooled and treated with 0.804 g (3 mmol) of CH_2I_2 and heated at 70 ^oC for 4 h. After usual work-up, the product was isolated in 90 % yield. The yields using other alkaline carbonate were: K_2CO_3 82%, Na_2CO_3 67%, and with Li_2CO_3 49%.

***tert*-Butyl dimethyl-2-iodo-1,1,1-ethanetricarboxylate (18).** To a solution of 0.348 g (1.5 mmol) of **11** in 7.5 mL of DMSO was added 0.489 g of cesium carbonate. The mixture was stirred at 70 ^oC for 5 h, cooled to rt, and 1.206 g (4.5 mmol) of CH_2I_2 were poured in and the mixture stirred at 70 ^oC for 12 h. The solution was diluted with 20 mL of ethyl acetate, the organic phase washed with saturated solution of ammonium chloride (10 mL) and brine (10 mL), dried and evaporated to yield 0.513 g (92%) of the product as a colorless oil. An analytical sample was obtained by column chromatography. HRMS Calcd. for $C_{11}H_{17}INaO_6$: 394.99620. Found: 394.99679. (Source Type ESI, Ion Polarity Positive) ^1H NMR ($CDCl_3$) δ : 1.49 (s, $C(CH_3)_3$, 9H), 3.67 (s, I-CH_2, 2H), 3.83 (s, OCH_3, 6H). ^{13}C NMR ($CDCl_3$) δ : - 0.14 (I-**C**H_2), 27.70 (**C**H_3), 53.37 (O-**C**H_3), 66.23 (**C** 4^o), 84.47 (**C**Me_3), 163.37(**C**O_2 ^{t}Bu), 165.62 (**C**O_2Me).

Benzyl dimethyl 2-iodo-1,1,1-ethanetricarboxylate (19). To a solution of 0.208 g (1 mmol) of **12** in 5 mL of DMSO was added 0.326 g of cesium carbonate. The mixture was stirred at 70 ^oC for 5 h, cooled to rt and treated with 0.804 g (3 mmol) of CH_2I_2. The mixture was stirred at 70 ^oC for 12 h, diluted with 20 mL of ethyl acetate, and the organic phase washed with aqueous 2 % HCl and brine, dried and evaporated to yield 0.283 g (74%) of product as a colorless oil. An analytical sample was purified by column chromatography. Anal. Calcd. for $C_{14}H_{15}IO_6$: C, 41.36; H, 3.72;.I, 31.21. Found: C, 41.5; H, 3.85; I, 31.02. HRMS Calcd. for $C_{14}H_{15}INaO_6$: 428.98055. Found: 428.97894.^1H NMR ($CDCl_3$) δ : 3.70 (s, I-CH_2, 2H), 3.77 (s, OCH_3, 6H), 5.25 (s, CH_2-Ph, 2H), 7.35 (m, Ph, 5H). ^{13}C NMR ($CDCl_3$) δ : - 0.42 (I-**C**H_2), 53.56 (O-**C**H_3), 65.84 (C 4^o), 68.36 (**C**H_2-Ph), 128.30 (C2',C6'-Ph), 128.57 (C4'Ph and C3',C5'Ph), 134.61 (C1'Ph), 164.45 (**C**O_2CH_2-Ph), 165.10 (**C**O_2Me).

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Supplementary Materials

Include ^1H and ^{13}C NMR spectra, GC-Mass spectra and IR spectra of selected examples appearing with the Paper.

References and Notes

1. Simonsen, J. L. *J. Chem. Soc*. **1908**, *93*, 1777.
http://dx.doi.org/10.1039/CT9089301777
2. Dowd, P.; Shapiro, M. *J. Am. Chem. Soc*. **1976**, *98*, 3724.
http://dx.doi.org/10.1021/ja00428a065
3. Guthzeit, M.; Dressel, O. *Berichte* **1888**, *21*, 2233.
4. Guthzeit, M.; Dressel, O. *Liebigs Annalen der Chemie* **1890**, *256*, 171.
http://dx.doi.org/10.1002/jlac.18902560108
5. Perkin, W.H.; Prentice, B. *J.Chem.Soc*. **1891**,59, 990.
http://dx.doi.org/10.1039/CT8915900990
6. Tutin, F. *J.Chem.Soc*. **1907**, *91*. 1141.
http://dx.doi.org/10.1039/CT9079101141
7. Zielinsky, N. *Berichte*. **1889**, 22, 3294.
8. Auwers, K, Thorpe, J. F. . *Liebigs Annalen der Chemie*. **1895**, *285*, 310.
http://dx.doi.org/10.1002/jlac.18952850304
9. Kötz, A,; Zörnig, W. *J. Prakt. Chem*. **1906**, *74*, 425.
http://dx.doi.org/10.1002/prac.19060740130
10. Padgett, H. C.; Csendes, I. G.; Rapoport, H. *J. Org. Chem*. **1979**, *44*, 3492.
http://dx.doi.org/10.1021/jo01334a009
11. Corson, B. B.; Sayre, J. L. *Org. Synth., Coll. Vol. II*. **1943**, 596.
12. Ferreira, P. C.; Miyata, Y. *An. Fac. Farm. Odont. Univ. S. Paulo* **1962**, *19*, 45.
13. Miyata, Y.; Ferreira, P.C. *Rev. Fac. Farm. Bioquim. S. Paulo* **1967**, 5, 305.
14. Böhme, H.; Háfner, L. *Chem. Ber*. **1966**, 99, 281.
http://dx.doi.org/10.1002/cber.19660990144
15. Prelicz, D.; Witek, H.; Wyzgowska, L. *Rocz. Chem*. **1967**, *41*, 267. *Chem. Abstr.* **1967**, *67*, 11147n.
16. Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; 3rd Edn. WILEY-VCH, Weinheim. 2003. Ch. 3.
17. Cope, A. C.; Holmes, H. L.; House, H. O. *Org. Reactions* **1957**, *9*, 139.
18. The iodocompounds **15**, **18**, and **19** react with zinc dust in THF to form the respective zinc homoenolates that can be reacted with electrophiles. Thus, for example, the zinc homoenolate of **15** treated with diluted acid solution yields 85% of **13** and, previous transmetallation with Knochel couprate (CuCN.2 LiCl) reacted with benzoyl chloride to give 60% of trimethyl 3-oxo-3-phenyl-1,1,1-propanetricarboxylate (unpublished results). Similar yield was obtained in an alternative way from **10a** and bromoacetophenone.[14]
19. Miyano, S,; Hashimoto. H. *Bull.Chem.Soc. Japan* **1971**, *44*, 2864.